95. The method of claim 91, wherein the agent inhibits tyrosine phosphorylation of the cytokine receptor γ chain.

96. The method of claim 91, wherein the agent inhibits tyrosine phosphorylation of both the cytokine receptor γ chain and a JAK kinase having a molecular weight of about 116 kD as determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis.

Please add the following new claims:

--97. The method of claim 50, wherein the T cell is contacted with the agent *in vitro*.

98. A method for modulating responsiveness in a T cell predetermined to be anergic, comprising contacting said T cell with an agent which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is modulated.

99. The method of claim 98, wherein the agent stimulates a signal associated with ligation of the cytokine receptor γ chain, such that T cell stimulation occurs.

100. The method of claim 99, wherein the agent acts extracellularly to stimulate a signal associated with ligation of the cytokine receptor γ chain such that the T cell is stimulated.

101. The method of claim 99, wherein the agent is an anti-γ chain antibody.--

REMARKS

The amendment and/or cancellation of claims in this application is for the purpose of expediting prosecution of the above-identified application and the amendment of the claims should in no way be construed as an acquiescence to the Examiner's rejection. Applicants reserve the right to pursue claims of the same or similar scope in this or another application.

Support for the amendments to claim 48 can be found in the specification, for example, at least at page 3, line 15 and Example 3. Support for the amendment to claim 50 can be found in the specification, for example at page 2, line 11. Support for new claim 97 can be found in the specification, for example, at page 3 line 24 or 27. Support for new claim 98 can be found in the specification, for example at page 3, beginning at line 10. No new matter has been added.

Restriction Requirement Under 35 U.S.C. § 121

The Examiner has deemed the restriction requirement to claims 48-61 proper and has made the requirement final. Applicants believe the restriction requirement under 35 U.S.C. §121 to be improper on the grounds that Applicants have presented an allowable generic claim which encompasses the species of activation (claims 49-70) and inhibition (claims 71-96) of a T cell response. Specifically, Applicants have presented a generic linking claim, claim 48, drawn to a method for modulating a response by a T cell. Claim 48 is generic to the species of both activation (claims 49-70) and inhibition (claims 71-96) of a T cell response. Applicants believe that a species election, i.e., methods for stimulating proliferation of a T cell using an agent which acts extracellularly to inhibit delivery of a signal through a cytokine gamma chain and wherein the agent is an anti–γ chain antibody (claims 48-52, and 54-61), is proper for searching purposes only, posing no undue burden on the Examiner. However a restriction under 35 U.S.C. § 121 is improper for above-stated reasons. ***Accordingly, Applicant hereby affirms the election of Group I (claims 48-96), the species of stimulating proliferation of a T cell using an agent which acts extracellularly to inhibit delivery of a signal through a cytokine gamma chain and wherein the agent is an anti–γ chain antibody (claims 48-52, and 54-61)***.

It is the Applicants' understanding that under 35 U.S.C. §121, an election of a single species for prosecution on the merits is required, to which the claims will be

B

restricted if no generic claim is finally held allowable. Applicants submit that claim 48 is generic. Applicants further understand that upon the allowance of a generic claim, he will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.41.

Objection to the Title of the Specification

The Examiner has objected to the title of the invention as not descriptive. This objection is respectfully traversed on the grounds that it is the Applicants' position that the present invention is drawn methods of stimulating and inhibiting T cell activation by manipulating the γ chain shared by several of the cytokine receptors. Accordingly, the term "modulating" in the title accurately describes the invention claimed in the above identified application. Therefore, Applicants respectfully request that the objection be reconsidered and withdrawn.

Objection to the Specification and Rejection of Claims 48-61 Under 35 U.S.C. §112, First Paragraph

The Examiner objects to the specification and rejects claims 48-61 under 35 U.S.C. §112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. It is the Examiner's position that *in vitro* and animal model studies have not correlated well with *in vivo* clinical trial results in patients and it is not clear that reliance on the *in vitro* experimental conditions accurately reflects the relative efficacy of the claimed therapeutic strategy to stimulate T cells, (inhibit unresponsiveness). The Examiner maintains that pharmaceutical therapies are unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect, (2) the protein may not reach the target area, or (3) other functional properties, known or unknown, may

B

make the protein unsuitable for *in vivo* therapeutic use. The Examiner states that there is no evidence that such an experimental model mimics the clinical situation; therefore, the predictive value of such an *in vitro* model remains unknown. The Examiner further argues that Applicants do not provide sufficient information or "nexus" of how to use the information gathered using T cell lines in a a clinical situation. It is the Examiner's position that administration of cytokines *in vivo* is complex.

Applicants respectfully traverse this objection to the specification and rejection of claims 48-61 for at least the following reasons. It is respectfully submitted that the relevant question is whether the specification "adequately teaches one of ordinary skill in the art how to make or use ***the claimed invention***". It is not necessary for Applicants to provide *in vivo* data as to whether the method of the instant invention can be used for the treatment of human disease, but rather Applicants must adequately teach the ordinarily skilled artisan how to make or use the claimed invention, e.g., use the methods being claimed. The pending claims are drawn to the modulation of T cell responsiveness. Claim 48 as amended is drawn to methods for modulating T cell responsiveness by use of an agent which modulates a signal associated with a cytokine receptor γ chain, such as an anti-γ chain antibody, to thereby modulate T cell responsiveness. It is the Applicants' position that recited "contacting" step can be performed either *ex vivo* or *in vivo*; *in vivo* modulation of responses is not a requirement of the claims.

Applicants respectfully submit that the disclosure provides a detailed description of agents within the scope of the claims which can be used in methods of *ex vivo* or *in vivo* therapy. Specifically, beginning at page 6, the cytokines IL-2, IL-4, and IL-7 are taught to stimulate through γc. Anti-γ chain antibodies are also taught to transduce a stimulatory signal via the common γ chain. In addition, teachings are provided which enable making peptide fragments of these agents or selecting peptide mimetics or small molecules that bind to γc. Teachings with regard to agents which inhibit signaling via γc are also provided, beginning at page 13 of the specification as filed. Screening assays

which can be used to identify other agents are described beginning at page 20 of the instant specification.

Applicants further submit that the specification provides teachings which would enable one of ordinary skill to modulate T cell responsiveness within the scope of the claims. For example, beginning at page 14 *in vitro* and *in vivo* therapies for the treatment of subjects are described. The specification provides teachings which enable the use of γc stimulatory agents, for example, to treat cells from subjects with tumor cells or infections, as well as the use of γc inhibitory agents to treat cells from subjects with, for example, GVHD, autoimmunity, allergy as described beginning at page 15 of the specification. Finally, teachings which enable pharmaceutical administration of modulating agents are also provided, beginning at page 18.

Moreover, the specification provides specific, working examples of the use of several of such agents which enables the ordinarily skilled artisan to practice the methods of modulation as claimed in the invention. For example, the teachings of Example 1 at page 22, show that IL-2, IL-4, and IL-7 can each prevent the induction of anergy which occurs after T cell receptor-mediated stimulation in the absence of a costimulatory signal. Example 2 at page 23 teaches that crosslinking of γc with antibody can also prevent the induction of anergy. Thus, the instant application does teach methods for modulating T cell responsiveness as claimed.

The standard for establishing therapeutic utility of biotechnological inventions under 35 U.S.C. § 112, first paragraph, was recently addressed by the CAFC in the case of *In re Brana*, 51 F.3d 1560; 34 U.S.P.Q.2D 1437 (CAFC, decided March 30, 1995). In this case, the CAFC held that

> [a] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must be taken as in compliance with the enabling requirement of the first***

B

> ***paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.*** In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (CCPA 1971) (emphasis added).
>
> From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Id. at 224, 169 U.S.P.Q. (BNA) at 370. ***Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.*** See In re Bundy, 642 F.2d 430, 433, 209 U.S.P.Q. (BNA) 48, 51 (CCPA 1981) (emphasis added).

In summary, the essence of the Court's decision was that if a patent disclosure contains a teaching of how to make and use an invention which is commensurate with the scope of the claims and, further provides specific working examples in support of the stated utility which then further evidence should ***not*** be required to satisfy the enablement requirement of section 112, first paragraph, ***unless there is reason to doubt the objective truth of the statements contained in the disclosure which are relied on for enabling support.*** Applicants submit that the present disclosure fully satisfies the enablement standard set forth in *In re Brana* in that it provides more than a sufficient teaching of how to make and use the claimed invention and further provides working examples demonstrating the *in vitro* efficacy of the claimed invention which, together, render credible the asserted use of the claimed methods for *ex vivo* or *in vivo* treatment of human disease states.

It is the Examiner's position that Applicants' methods are drawn to treating pathological conditions associated with tumor, pathogens, bacteria and viruses, but that these conditions are diagnosed and treated after tumor or infectious agents are already in place. The Examiner states that Applicants have not provided sufficient evidence that indicates that there is window of opportunity to inhibit unresponsiveness and that generally, such diseases are diagnosed only after significant pathology has occurred. This rejection is respectfully traversed. Again, Applicants draw the Examiner's attention to the claims as pending, which do not require any specific therapeutic end points. Specifically,

B

the claims are drawn to methods for modulating T cell responsiveness by contacting a T cell with agents which modulate signaling via the common γ chain; no *in vivo* end point is claimed. Again, it is the Applicants' position that this is a credible utility for the treatment of these disease states. Moreover, Applicants contend that the growing evidence that costimulatory molecule can augment tumor immunity indicates that T cell unresponsiveness does contribute to certain disease states and further supports the utility claimed by Applicants (see, for example Baskar et al. 1993 *Proc. Natl. Acad. Sci. USA.* 90:5687, Attached as Appendix A). Furthermore, with regard to unexamined claims (claims 71-96, which are drawn to inhibiting T cell responsiveness) applicants also point out that anergy can be induced in a subject's T cells prior to the exposure of the subject to that antigen.

It is also the Examiner's position that there is insufficient evidence of an appropriate agent other than γc-specific antibodies, IL-4 and IL-7; as Applicants' evidence indicates other agents do not inhibit unresponsiveness. The Examiner indicates that Applicants should limit claims to these agents. This rejection is respectfully traversed. Applicants refer the Examiner to the discussion herein with respect to Applicants' teachings of agents within the scope of the invention. Further to that discussion, in addition to γc specific antibodies, IL-4 and IL-7, Applicants also provide experimental data which demonstrates that IL-2 can prevent unresponsiveness (see, for example, Example 1) and the fact that IL-13 and IL-15 signal via γc is also disclosed at page 25 of the specification. The use of mimetics and small molecules and methods for screening assays to identify other agents which signal via γc is also taught in the specification. Therefore, it is the Applicants' position that claims should not be limited to anti- γc antibodies, IL-4 and IL-7.

The Examiner is of the opinion that the specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering an agent which modulates a signal associated with ligation of the cytokine

B

receptor γc. The Examiner indicates that the specification does not teach how to extrapolate data obtained from *in vitro* assays associated with the molecular mechanisms of unresponsiveness in T cell links to the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention. This rejection is traversed for the reasons detailed above. Furthermore, it is the Applicants' position that it would require only routine experimentation by one of ordinary skill in the art to determine appropriate *in vivo* therapeutic regimens based on the present disclosure and the teachings in the art. In Cross v. Iizuka (753 F.2d 1040 (Fed. Cir. 1985) the court found that "[t]he enablement requirement's how-to-use aspect was met even though a patent specification did not disclose dosage levels for the invention...because (1) the disclosed utility was to demonstrate pharmacological activity in an *in vitro* environment... and (2) one skilled in the art could determine the dosage level without undue experimentation." Moreover, as indicated above, the instant specification does enable the therapeutic uses of the claimed methods. Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims 48-61 Under 35 U.S.C. §112, First and Second Paragraphs

The Examiner rejects claims 48-61 under 35 U.S.C. §112, first and second paragraphs, asserting that the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the invention, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner finds claims 48-61 indefinite in the entire recitation of base claim 48 as well as the phrases "modulating unresponsiveness by a T cell", "unresponsiveness by the T cell is inhibited", and "under conditions which normally result in unresponsiveness in a T cell". It is the Examiner's position that the claims are vague and indefinite because the language is confusing and inappropriate for the claimed therapeutic endpoints. The Examiner indicates that the

B

claims should reflect the elected invention, which is simply methods of stimulating T cells rather than by applying a double negative, that is, inhibiting unresponsiveness.

It is respectfully submitted that the above rejection does not pertain to the claims as newly amended. The language "unresponsiveness by a T cell is inhibited" and "under conditions which normally result in unresponsiveness in a T cell" have been removed from the claims. The amendment to the claims was made for the purpose of expediting prosecution of the above-identified application and should in no way be construed as an acquiescence to the Examiner's rejection. It is Applicants' position that the language "unresponsiveness by a T cell is inhibited" and "under conditions which normally result in unresponsiveness in a T cell" was art recognized terminology at the time the claimed invention was made and the ordinarily skilled artisan would have known what was meant by such language. Applicants reserve the right to pursue a claim with this language in this application or another application. This rejection is traversed to the extent that it is the Applicants' position that "modulating T cell responsiveness" as used by Applicants is sufficiently definite and is meant to encompass the species of T cell stimulation and T cell inhibition. Applicants have amended several of the pending claims and believe that the amendment submitted concurrently herewith more clearly defines the invention.

The Examiner also finds the word "unresponsiveness" to be indefinite since, he contends, unresponsiveness in immunology can refer to immunological tolerance. It is the Examiner's position that tolerance is not necessarily associated with the claimed therapeutic endpoints of tumors and pathogens. The Examiner states that although tumors may not be rejected because they are viewed as self which in turn would be immunological tolerance; this occurs at the fetal/neonatal stages of life and is not the same for adult animals and Applicant's invention is drawn to treating diseases in adult animals.

This rejection is traversed to the extent that the specification clearly indicates that the present invention is directed towards modulating responsiveness in a T cell which has

B

received receptor-mediated stimulation in the absence of costimulatory signals and not directed towards T cell tolerance as indicated at pages 2 and 3. The difference between neonatal tolerance and anergy resulting from T cell receptor stimulation in the absence of costimulation is art recognized. Furthermore, the word "unresponsiveness" has been removed from the claims.

It is the Examiner's position that Applicants refer to unresponsiveness as a lack of costimulation, but that it is not clear the costimulation alone is responsible for the disease processes targeted. The Examiner further contends that conditions which normally result in unresponsiveness are ill-defined and only appear to reflect tumors or pathogens. This rejection is respectfully traversed. The pending claims are drawn to methods of modulating T cell responsiveness. Applicants submit that it is not necessary that a lack of costimulation, or insufficient costimulation, be responsible for every instance, nor be the sole factor causing, cancer or reduced immune response to a pathogen. Applicants' teachings in combination with the state of the art at the time the claimed invention was made demonstrate that a lack of costimulation is involved in a variety of diseases including cancer, see for example, Baskar et al., submitted herewith.

Finally, the Examiner contends that since Applicants' invention is drawn to stimulating T cells to alleviate any lack of costimulation, Applicants should claim what the invention is, that is, methods for stimulating T cells. It is the Examiner's position that modulation is not appropriate because modulation can occur both in positive and negative directions and applicant elected methods of stimulating T cells. The Examiner instructs the Applicants to amend the claims from their current confusing language to a clear positive recitation of the elected and claimed methods.

It is the Applicants' position that it is not necessary for the claims to be limited to the elected species in that Applicants are entitled to pursue generic claims, such as claim 48, which encompass the elected species. Applicants respectfully request that the rejection be withdrawn.

B

Rejection of Claims 48-61 and 56-57 Under 35 U.S.C. §112, Second Paragraph

The Examiner rejects claims 48-61 and 56-57 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is the Applicants' position that the amendment submitted concurrently herewith more concisely claims the Applicants' invention and obviates this rejection.

It is also the Examiner's position that claims 56-57 are indefinite in that their recitation does not further limit the claimed methods. Claim 56 had been amended to properly depend from claim 48, thus Applicants request reconsideration and withdrawal of this rejection.

Rejections Under 35 U.S.C. §102

A. Rejection of Claims 48-53, 55-58, and 60-61 under 35 U.S.C. §102(e)

Claims 48-53, 55-58, and 60-61 stand rejected under 35 U.S.C. §102(e) as being anticipated by Plunkett et al. (U.S. Patent No. 5,382,427). The Examiner characterizes Plunkett et al. as teaching the use of IL-4 to treat tumors. Applicants submit that the reference teaches only the treatment of solid tumors with IL-4. This reference fails to teach or suggest detecting signaling via a common γ chain or predetermining whether a T cell in unresponsive prior to treatment with IL-4 as required by the claims as amended. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

B. Rejection of claims 48-53 and 55-61 under 35 U.S.C. §102(b)

The Examiner rejects claims 48-53 and 55-61 are rejected under 35 U.S.C. §102(b) as being anticipated by Lee et al. (U.S. Patent No. 5,017,91). The Examiner indicates that Lee et al. teaches the use of IL-4 to enhance the natural defense against

various infections and malignancy. It is the Applicants position that this reference discloses compositions of matter, namely IL-4 and mutated forms of IL-4. This reference fails to teach or suggest that IL-4 can stimulate the common γ chain or that blockade of the common γ chain could induce unresponsiveness. The only disclosure in the reference with regard to the use of the claimed compositions is made in column 2 at line 41 where it is stated that "One hope is that the levels of lymphokines in a patient can be manipulated directly or indirectly to bring about a beneficial immune response, e.g. suppression in the case of inflammation, allergy, or tissue rejection, or stimulation or potentiation in the case of infection or malignant growth". This "hope" does not enable one of ordinary skill in the art to be able to modulate the response of a T cell. The reference provides no teaching as to how IL-4 could be both stimulatory and inhibitory. At column 20 line 51 the reference states that the polypeptides of the present invention may be used "to enhance natural defense against various infections. Thus, patients with rheumatoid arthritis, in need of a transplant, or with immunodeficiency caused by cancer chemotherapy, advanced age, immunosuppressive agents, etc., may be treated with such polypeptides. The compositions can selectively stimulate the immune system...." The reference does not teach or suggest to one of ordinary skill in the art each and every element of the rejected claims, and further does not provide an enabling disclosure. Since a reference must be enabling in to be prior art, this reference in not an effective reference under §102(b). Moreover, this reference fails to teach or suggest detecting signaling via a common γ chain or predetermining whether a T cell in unresponsive prior to treatment with IL-4 as required by the claims as amended. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

C. Rejection of Claims 48-53 and 55-61 under 35 U.S.C. §102(a)(e)

Claims 48-53 and 55-61 stand rejected under 35 U.S.C. §102(a)(e) as being anticipated by Lynch et al. (U.S. Patent No. 5,229,115). The Examiner indicates that

Lynch et al. teach the use of IL-7 in the treatment of an individual with cancer or a viral infection by adoptive immunotherapy with T cells in the presence of IL-7. It is the Applicants position that this reference teaches the activation of cytotoxic T lymphocytes with IL-7 *ex vivo*. This reference fails to teach or suggest detecting signaling via a common γ chain or predetermining whether a T cell in unresponsive prior to treatment with IL-7 as required by the claims as amended. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejection of claims 48-53, 59, and 61 under 35 U.S.C. §102(e)

The Examiner rejects claims 48-53, 59 and 61 under 102 (e) as being anticipated by Grabstein et al. (U.S. Patent No 5,464,769) who teach a method of treating microbial infections in a microbially infected mammal by administering IL-7. The reference discloses the use of IL-7 to stimulate mononuclear phagocytes, not to modulate the responsiveness of a T cell. This reference fails to teach or suggest detecting signaling via a common γ chain or predetermining whether a T cell in unresponsive prior to treatment with IL-7 as required by the claims as amended. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

New Claims 98-101

Applicants have added a new generic claim, claim 98, which encompasses the elected species and is believed to be free of the prior art. None of the art made of record teaches or suggests modulating T cell responsiveness in a T cell predetermined to be anergic by contacting the T cell with an agent that signals via the common γ chain. Applicants have also added claims 99-101, which depend from claim 98, and are drawn to the elected species of T cell stimulation (claim 99), an agent which acts extracellularly (claim 100), and an anti-γ chain antibody (claim 101). All of the newly added claims are

believed to be free of the prior art and it is respectfully suggested that claims 98-101 be allowed.

Claims Free of the Art

Applicants gratefully acknowledge that claim 54 has been found by the Examiner to be free of the prior art.

CONCLUSION

In view of the foregoing arguments, reconsideration and allowance of claims 48-101 is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

By Jane Remillard Reg. No. 38,872
for: Amy E. Mandragouras
Reg. No. 36,207
Attorney for Applicant

LAHIVE & COCKFIELD
60 State Street
Boston, MA 02109
(617) 227-7400

Dated: September 18, 1996

B